PEDIATRIC FORMULATIONS: NIH-FDA COOPERATIVE EFFORTS

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NATIONAL INSTITUTES OF HEALTH

OUTLINE

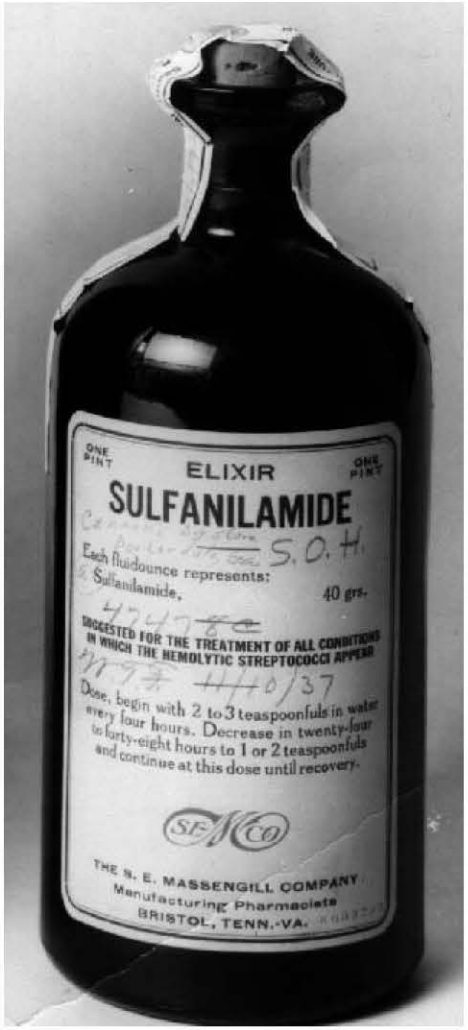
- Need for Improved Oral Pediatric Formulations
- Best Pharmaceuticals for Children Act
- NICHD Efforts: NICHD-FDA Intra-Agency Agreement for an Oral Formulations Platform

Article (from the 1906 Congressional Record)	Determination
Gray's Catarrh Powder	Contains cocaine
Shiloh's Consumption Cure	Contains chloroform and alcohol
Hood's Sarsaparilla	Contains 17.02% alcohol by volume
Paine's Celery Compound	Contains 20.24% alcohol by volume
Piso's Consumption Cure	Contains chloroform, alcohol, and marijuana
Dr. Bull's cough syrup	Contains chloroform and morphine
Mrs. Winslow's Soothing Syrup	Contains morphine, some samples contained higher concentrations of the drug
Dr. King's Consumption Cure	Contains morphine and chloroform
Dr. Mile's new cure for the heart	10.83% alcohol by volume

CHLOROFORM, ALCOHOL, MARIJUANA

MORPHINE

DIETHYLENE GLYCOL



HISTORY OF PEDIATRIC DRUG TRAGEDIES

- 1905: deaths from patent medicines
- 1936: sulfanilamide dissolved in diethylene glycol kills 107
- 1961: thalidomide causes limb deformities

REGULATORY ACTS

- **1906**: Pure Food and Drug Act
  - Labels of food and drugs must truthfully identify contents (pure)
- **1937**: Federal Food, Drug, and Cosmetic Act
  - Drugs must be safe
- **1962**: Kefauver-Harris Amendment
  - Drugs must be effective for their labeled indication

BEST PHARMACEUTICALS FOR CHILDREN ACT: NIH

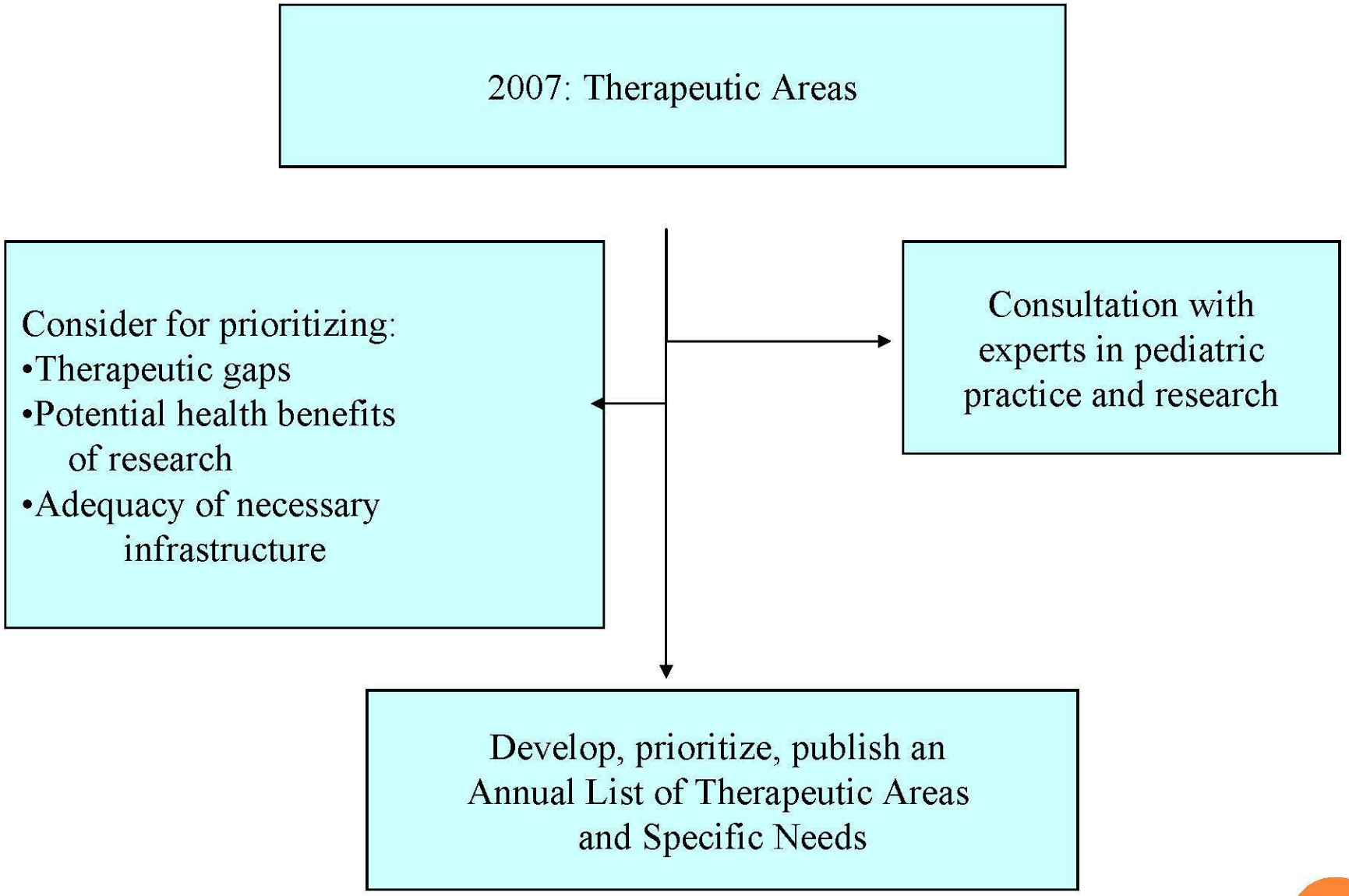
- Prioritize drugs/therapeutic areas
- Sponsor pediatric clinical trials
- Submit data to FDA for labeling changes

2002: Master List of all Off-Patent Drugs which lack adequate pediatric labeling

Consider for prioritizing:
- Availability of S/E data
- Are additional data needed?
- Will new studies produce health benefits?
- **Reformulation?**

Consultation with experts in pediatric practice and research

Develop, prioritize, publish an Annual List of Drugs


2007: Therapeutic Areas
Consider for prioritizing:
•Therapeutic gaps
•Potential health benefits of research
•Adequacy of necessary infrastructure
Consultation with experts in pediatric practice and research
Develop, prioritize, publish an Annual List of Therapeutic Areas and Specific Needs

PRIORITIZATION

- Many drugs and therapeutic areas

CLINICAL TRIALS

- Lorazepam for sedation
- Lorazepam for status epilepticus
- Nitroprusside for blood pressure reduction
- Baclofen (oral) for spasticity **(re-formulation)**
- Lithium for mania
- Meropenem for severe intra-abdominal infections in neonates (volume)
- Azithromycin for Ureaplasma infections
- Morphine for pain in neonates

CLINICAL TRIALS

- NHLBI: Hydroxyurea in young children with sickle cell disease **(re-formulation)**
- **NCI:**
  - Vincristine for pediatric malignancies
  - Actinomycin-D for pediatric malignancies
  - Methotrexate and neuro-cognition
  - Daunomycin disposition related to body mass
  - Isotretinoin for neuroblastoma **(re-formulation)**

INFRASTRUCTURE: PEDIATRIC TRIALS NETWORK

- Awarded September 28, 2010
- Duke University
  - https://www.fbo.gov/index?s=opportunity&mode=form&id=cf49c1b60b546914941b266295b24c84&tab=core&_cview=1
- Cores:
  - Management
  - Clinical trials performance
  - **Formulations development for clinical trials**
  - Clinical pharmacology study design and analysis
  - Device development (validation)

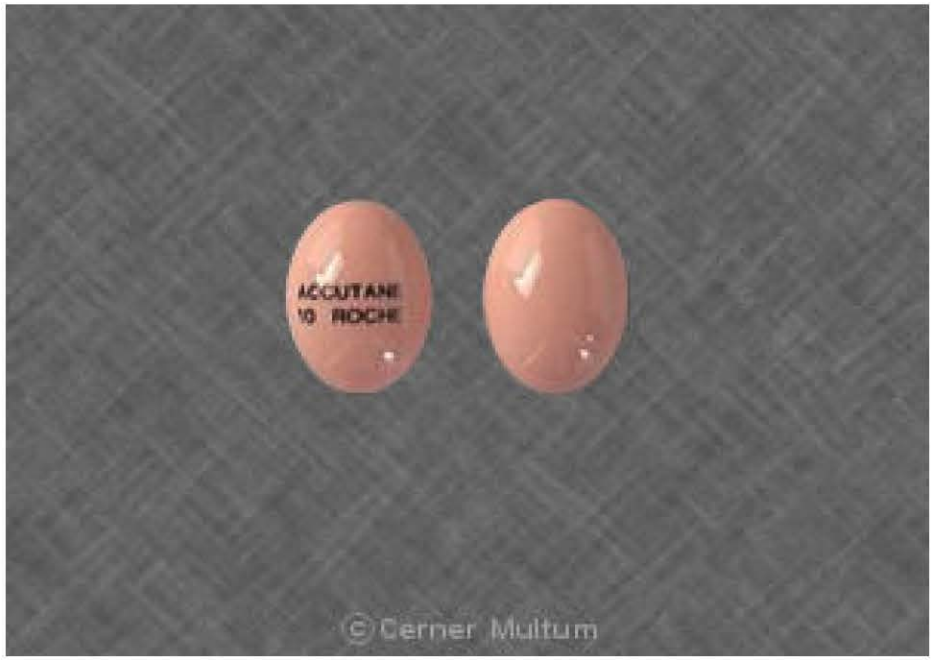
FORMULATIONS PROBLEMS WITH BPCA TRIALS

- Baclofen
- Hydroxyurea
- Meropenem
- Isotretinoin

HYDROXYUREA 500 MG

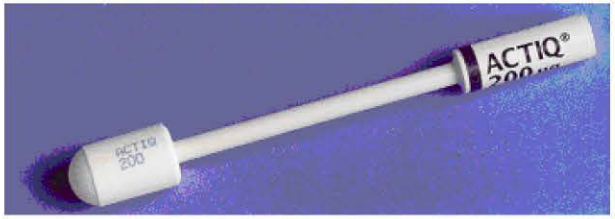
MEROPENEM VIAL

ISOTRETINOIN 10 MG



EXAMPLES OF CREATIVE FORMULATIONS

Dextromethorphan



Fentanyl

Courtesy J. Breitkreutz

PROBLEMS

- Inaccurate dosing
- Lack of stability
- Bad taste
- Adherence problems
- Lack of standardization in extemporaneous compounding
- Environmental safety from home compounding

IDEAL ORAL PEDIATRIC DOSAGE FORM

- Tasteless/taste-masked
- With minimal excipients
- In flexible dosage increments
- Orally dissolvable, or easy to swallow or dissolve in small amount of liquid
- Heat, humidity and light stable

DRUGS LACKING A PEDIATRIC FORMULATION

- Hydroxyurea
- Isoniazid
- 6-mercaptopurine, methotrexate, 6-thioguanine, isotretinoin
- L-thyroxine
- Clindamycin
- Prednisone, prednisolone
- Baclofen
- Antiretrovirals

- Meropenem (concentration, volume for neonates)

IN THE DEVELOPING WORLD

- Albendazole
- For malaria: sulfadoxine-pyrimethamine, chlorproguanil-dapsone, mefloquine
- For trypanosomiasis : benznidazole, nifurtimox

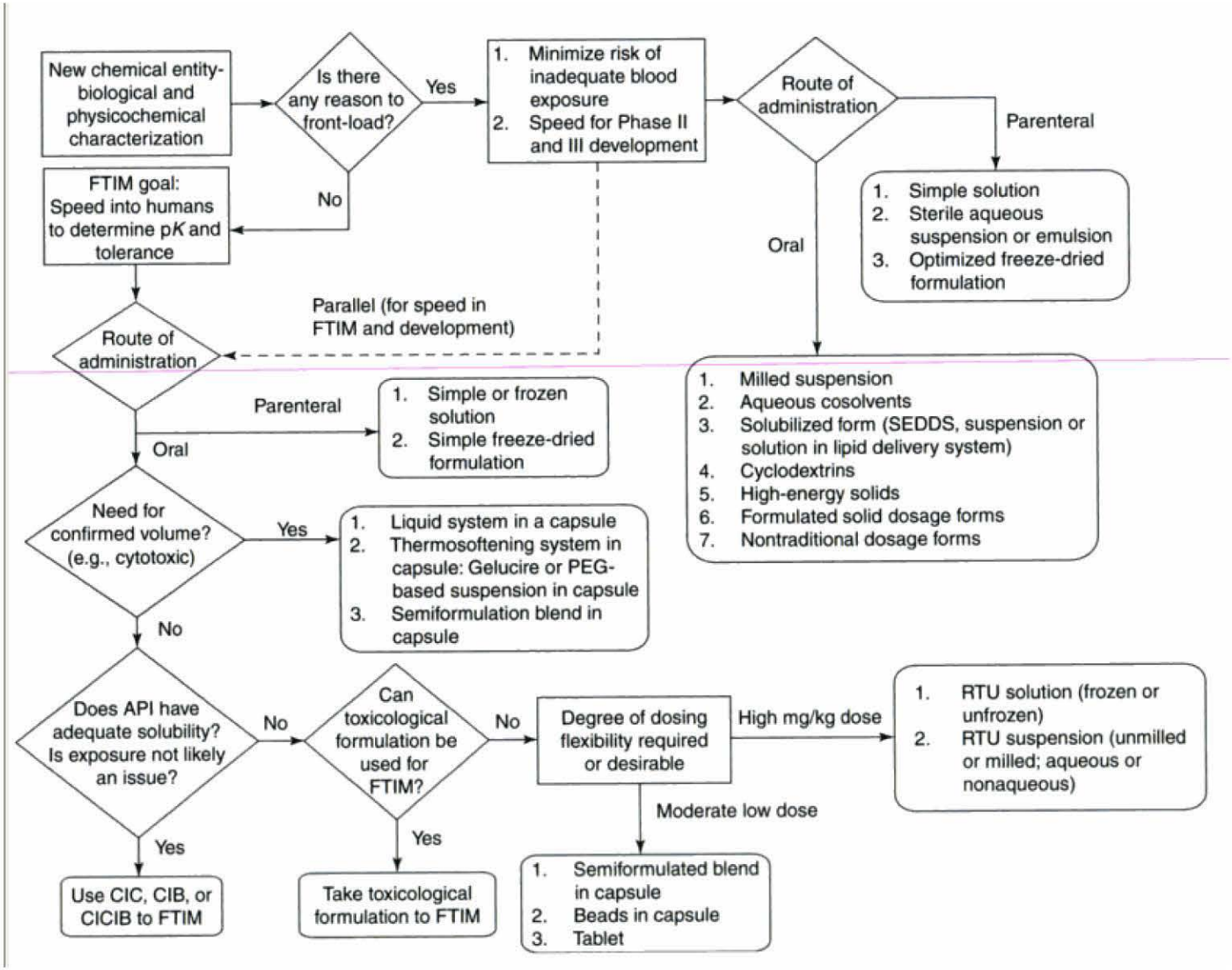
WATER, REFRIGERATION

PROBLEMS

- Technical/Scientific
- Business: potential population affected
  - Children
  - Persons with swallowing problems: elderly, stroke, cerebral palsy

WE NEED SUCH FLOW DIAGRAMS FOR PEDIATRICS

COURTESY JEFFREY BARRETT



PEDIATRIC FORMULATIONS 2012

NIH-FDA INTERACTIONS

- American Association of Pharmaceutical Scientists 2008
  - Formulation Design and Development
- Division of Product Quality Research Programs, FDA

NIH-FDA INTRA-AGENCY AGREEMENT: FORMULATIONS PLATFORM 2010-2012

- Provide open source, publicly available oral pediatric formulations platform
- Designate specific formulations technologies, given the molecular and chemical properties of the drug and the specific desired properties of the dosage form

TASKS

1- assess commercially available formulations

2- determine publicly available technologies

3- employ computational methods to prototypes to categorize molecular structures for various characteristics

- Solubility, permeability
- Stability
- Taste (bitterness)

TASKS

4- determine optimal formulations technologies for specific drug categories

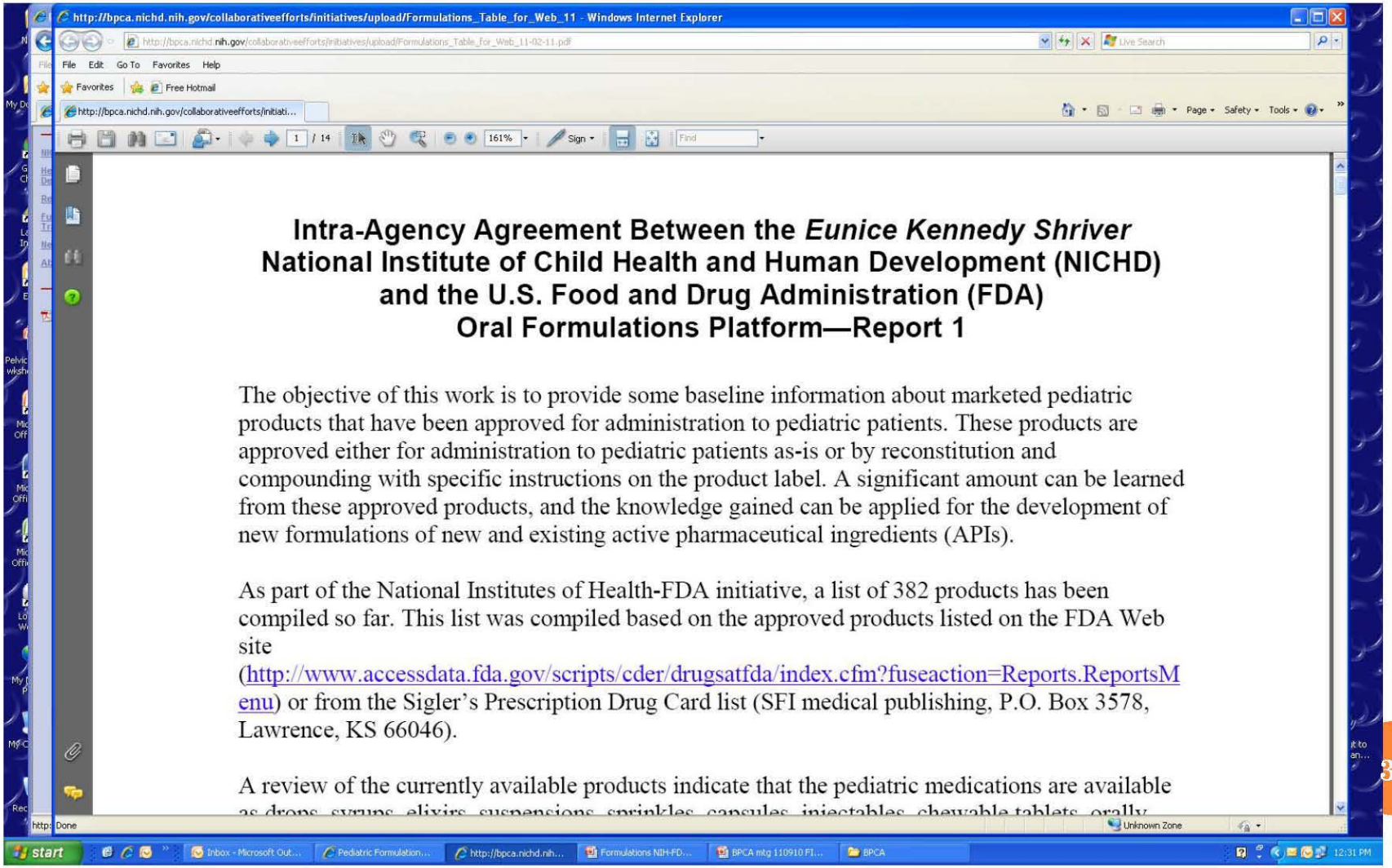
5-produce prototype batches using available technologies

6- present results in publications /presentations and on the NIH and FDA web sites

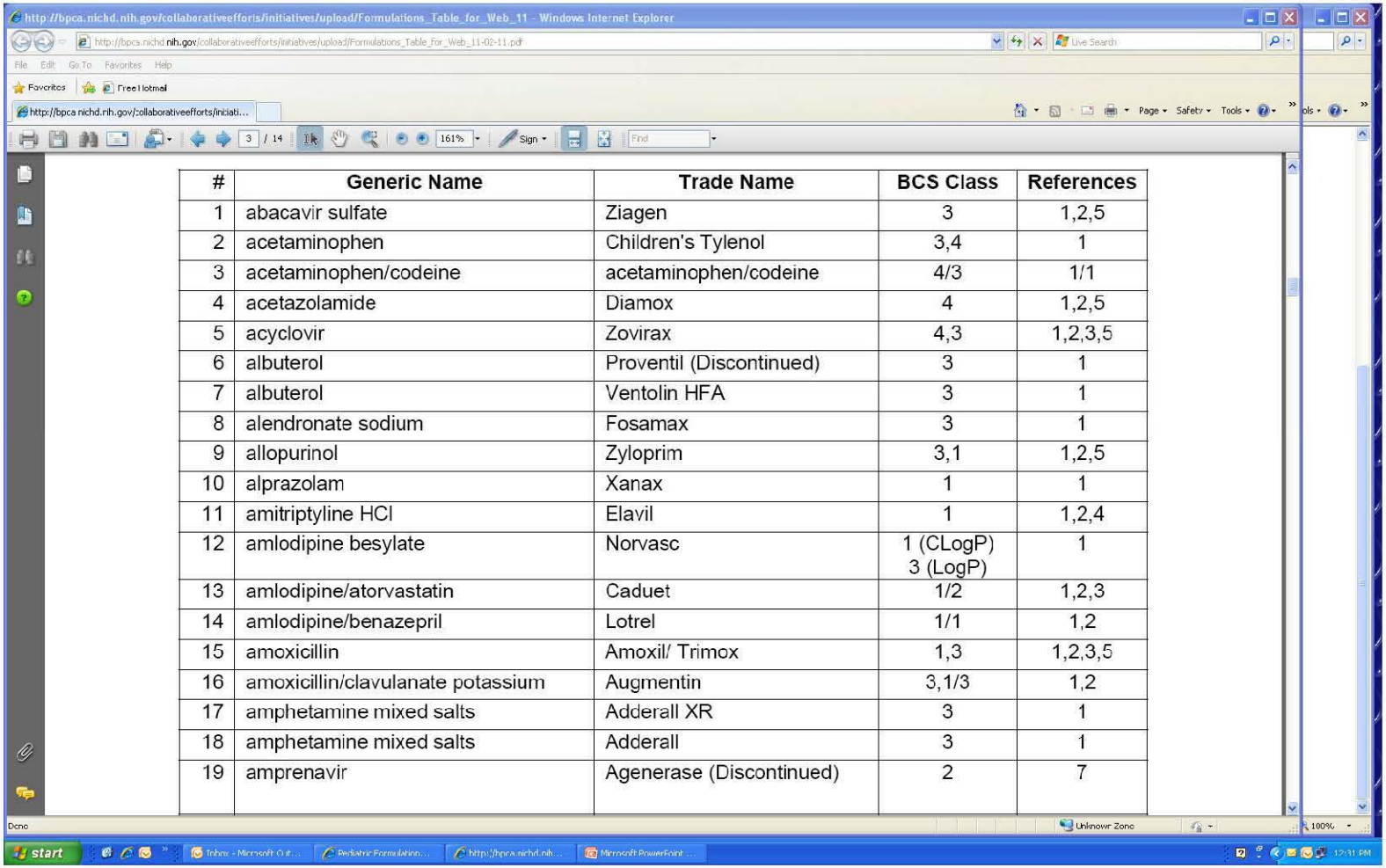
TASK 1 PUBLICALLY AVAILABLE

- http://bpca.nichd.nih.gov/collaborativeefforts/initiatives/index.cfm

TASK 1 PUBLICLY AVAILABLE ON WEB SITE



TASK 1: BCS TABLES



#	Generic Name	Trade Name	BCS Class	References
1	abacavir sulfate	Ziagen	3	1,2,5
2	acetaminophen	Children's Tylenol	3,4	1
3	acetaminophen/codeine	acetaminophen/codeine	4/3	1/1
4	acetazolamide	Diamox	4	1,2,5
5	acyclovir	Zovirax	4,3	1,2,3,5
6	albuterol	Proventil (Discontinued)	3	1
7	albuterol	Ventolin HFA	3	1
8	alendronate sodium	Fosamax	3	1
9	allopurinol	Zyloprim	3,1	1,2,5
10	alprazolam	Xanax	1	1
11	amitriptyline HCl	Elavil	1	1,2,4
12	amlodipine besylate	Norvasc	1 (CLogP) 3 (LogP)	1
13	amlodipine/atorvastatin	Caduet	1/2	1,2,3
14	amlodipine/benazepril	Lotrel	1/1	1,2
15	amoxicillin	Amoxil/ Trimox	1,3	1,2,3,5
16	amoxicillin/clavulanate potassium	Augmentin	3,1/3	1,2
17	amphetamine mixed salts	Adderall XR	3	1
18	amphetamine mixed salts	Adderall	3	1
19	amprenavir	Agenerase (Discontinued)	2	7

PROGRESS ON TASKS

1- **assess commercially available formulations: completed**

2- determine publicly available technologies

3- employ computational methods to prototypes to categorize molecular structures for various characteristics

- **Solubility, permeability: completed**
- Stability
- Taste (bitterness)

TASKS

4- determine optimal formulations technologies for specific drug categories

5-produce prototype batches using available technologies: three products reformulated

6- present results in publications /presentations and on the **NICHD BPCA and FDA web sites: completed tasks are on the NICHD BPCA and FDA web sites**

BENEFITS OF A FORMULATIONS PLATFORM

- Children and others with swallowing problems (elderly, stroke, cerebral palsy)
- FDA: facilitate the development of novel oral dosage forms
- Industry: transparent resource to inform and facilitate production of new oral dosage forms

NICHD FUNDING OPPORTUNITY ANNOUNCEMENTS: FORMULATIONS

- **Development of Appropriate Pediatric Formulations and Pediatric Drug Delivery Systems (**PAR 11-301, 302, 303, 304, 305)
  - The purpose of this Funding Opportunity Announcement is to address different and complementary research needs for the development and acceptability of pediatric drug formulations in different age groups. Development and testing of novel pediatric drug delivery systems is also part of this initiative.
  - http://grants.nih.gov/grants/guide/

CONTACT INFORMATION

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